Rabies risk

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Annual number of rabies death globally in 2015: 59,000 (95% CI, 25,000–159,000) deaths*
*probability decision-tree approach (community surveys, large-scale verbal autopsy surveys, active surveillance and contact tracing)
> 99% resulting from dog bites
> 40% in children < 15 years

Hampson et al., PLOS Neglected Tropical Diseases, 2015
WHO, WER, 2017

Human rabies geographical distribution
Number of rabies death globally in 2015

**TOP COUNTRIES**

- **ASIA:** INDIA (35%), CHINA, THE PHILIPPINES
- **AFRICA:** NO RELIABLE DATA
- **AMERICA:** HAITI & BOLIVIA
- **MIDDLE EAST:** YEMEN & IRAQ

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Rabies Bulletin Europe, 2013

Résurgence de la rage du renard en Italie (2008)

Résurgence de la rage du renard en Grèce (2012)

Travel-associated human rabies
60 cases in 1990-2012

10 new cases in 2013-2019

• Taiwan ex. Philippine (migrant)
• US ex. Guatemala (Migrant)
• The Netherlands ex. Haiti (not documented)
• The Netherlands ex. India (Indian married a Dutch)
• France ex. Mali (VFR)
• UK ex. India (not documented)
• France ex. Sri Lanka (Tourist)
• UK ex. Morocco (Tourist)
• Qatar ex. Nepal (Migrant)
• Norway ex. Philippines (Tourist)

• 2.6 cases per year, increase from 2004

Rabies cases among international travelers 1990-2015

Main points
• Adult travelers (83%)
• Men (75%)
• Residence in Europe (57%) and US (27%)
• Tourists + business + expatriates (57%) - VFR + migrants (43%)
• Dogs (85%)

• Mean incubation time 274 days (9 months)
• 9 case < 30 days
• 1 case 12 days after dog bite in India
• 1 case 15 days after bat bite in Mexico
• 1 case 5 years after immigration from China
• 1 case 8 years after dog exposure in Brazil
• 1 case 10 years after dog bite in Myanmar
• 8% rabies PEP in country of exposure, 100% mortality

Conclusions

• Diagnosis challenging with multiple missed diagnosis
  — Low index of suspicion
  — Negative history of animal bite
  — Atypical presentation (Guillain-Barré, sore-throat infection, orthopedic, acute psychiatric disorder…)
  — Long incubation time

Meta-analysis

• 1970-2008 (38 year period study)
• 9 published surveys
• > 1 270 000 tourists (denominator)
• > 11 000 expatriates (denominator)
• > 600 injured travelers
• Exposure in Africa, Asia, Latin America and The Middle East

The Steffen tree monthly incidence per 100 travelers

0.4% (our estimate)
• Most injured individuals reported to GeoSentinel are relatively young tourist travelers originating from developed countries, corresponding to the overall traveler population seen at GeoSentinel sites. **Travelers injured by potentially rabid animals do not present specific demographic characteristics compared to other ill travelers** and therefore targeting reinforcement of preventive measures cannot be based on demographic factors alone.

**Geographic destination** is the strongest determinant of rabies exposure in travelers and should be considered in preventive vaccination decisions.

Age, gender, reason for travel and duration of travel are not good indicators for risk-based decisions.

- 42% in South East Asia, 32% other Asian countries, 9% Africa, 7% Latin America, 3% Middle East: top countries: Thailand, Indonesia, Nepal, China, India.
- Median travel duration: 15 days (patients seen after travel), 20 days before presenting (patients seen during travel).
- Animal species: 60% dog, 24%, NHP, 10% cat, 2% bat.
- 2/3 of NHP exposure occurred in Asia, 90% occurred in tourists.

**Rabies in Nonhuman Primates and Potential for Transmission to Humans: A Literature Review and Examination of Selected French National Data**

**Rabies Postexposure Prophylaxis for Travelers Injured by Nonhuman Primates, Marseille, France, 2001–2014**
WHO Strategic Advisory Group of Experts (SAGE) on immunization


Human-to-human transmission of RABV is extremely rare. The only documented cases of human-to-human transmission occurred via tissue and organ transplants from RABV-infected individuals, and a single case of likely perinatal RABV transmission.

No case of human rabies resulting from consumption of raw meat or milk from a rabid animal has been documented.

RABV infection in rodents is very uncommon. No human rabies cases due to bites by rodents have been reported.

Risk assessment

The following categories describe the risk of a RABV exposure according to the type of contact with the animal suspected of having rabies:

- **Category I** touching or feeding animals, animal licks on intact skin (no exposure);
- **Category II** nipping of uncovered skin, minor scratches or abrasions without bleeding (exposure);
- **Category III** single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure).

Postexposure Prophylaxis (PEP)

- **PEP always** includes:
  - Wound washing and wound care
  - A series of rabies vaccine injections should be administered immediately after an exposure

- **PEP sometimes** includes:
  - Administration of rabies immunoglobulins (RIG)
    - in severe category III exposures
    - in category II exposures to bats
Vaccines

- Cell culture and embryonated egg-based rabies vaccines (CCEEVs) are intended for use in both pre-exposure prophylaxis (PrEP) and for post-exposure prophylaxis (PEP).
- Since 1984, WHO has strongly recommended discontinuation of production and use of nerve tissue vaccines and their replacement by modern, concentrated, purified CCEEVs.
- CCEEVs have been shown to be safe, highly immunogenic and well tolerated.

Vaccine administration

- Evidence supports administration of CCEEVs by intradermal (ID) or intramuscular (IM) injection.
- ID administration of rabies vaccines provides a cost-saving and dose-sparing alternative.
- A systematic review of vaccine potency has shown that current vaccines (> 2.5 IU/IM dose), when administered by the ID route for either PEP or PrEP, have efficacy equivalent to or higher than that of the same vaccine administered by the IM route.

Rabies immunoglobulins (RIG)

- After exposure to RABV, RIG provides passive immunization by neutralizing the virus at the wound site before the immune system can respond to the vaccine by producing VNAs.
- RIG is derived from human blood (hRIG) or equine blood (eRIG). They are considered to have similar clinical effectiveness.
- A single monoclonal antibody (mAb) product against rabies, licensed in India in 2017, has been demonstrated to be safe and effective in clinical trials.

For both PEP and PrEP, vaccines can be administered by either the ID or IM route.

- One ID dose is 0.1 mL of vaccine;
- One IM dose is 0.5 mL or 1.0 mL depending on the product, i.e. the entire content of the vial.

- If any doses are delayed, vaccination should be resumed, not restarted.
- A change in the route of administration or in vaccine product during a PEP or PrEP course is acceptable if such a change is unavoidable.
WHO Position: Recommended Schedules

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Dose</th>
<th>Schedule</th>
<th>Local Reaction</th>
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<tr>
<td>ESSEN</td>
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<tr>
<td>ZAGREB</td>
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</tbody>
</table>

Naive individual

**IM (1 ml)**

- ESSEN
  - D0
  - D3
  - D7
  - D14
  - D28
- ZAGREB
  - D0
  - D3
  - D7
  - D14
  - D21

- + RIG in category III exposure

**ID (0.1 ml)**

- D0
  - ID
  - (0.1 ml)
  - 4x RIG

- Not recommended anymore by WHO

Immunized individuals

**IM (1 ml)**

- D0
  - D3

**ID (0.1 ml)**

- D0
  - ID
  - (0.1 ml)

RIG is not indicated

WHO Position: Administration of rabies immunoglobulins (RIG)

- RIG should be administered only once, preferably at, or as soon as possible after, the initiation of PEP.
- RIG is infiltrated into and around the wound.
- For optimal effectiveness, the maximum dose calculation for RIG is 40 IU/kg body weight for equine derived RIG (eRIG) products, and 20 IU/kg body weight for human derived RIG (hRIG). Skin testing before eRIG administration should not be done because of unreliable prediction of adverse effects.

Did you know:

- Even if RIG is not available at the first visit (PEP day 0), RIG can be given up to day 7 after the first rabies vaccine administration.
Effective 100%

A few points

- PEP should be administered as soon as possible
- There is no time limit to administer PEP in case of type III exposure (however, if vaccine supply is limited, vaccine can be reserved for exposure that occurred within 12 months)
- There are no contra-indications to PEP
- In case of repeated exposure < 3 months after previous PEP, only wound treatment is required

For dog, cat and ferret-related injuries

- If the animal remains healthy for 10 days starting from the date of the bite, PEP can be discontinued

In any case

- When possible, suspect animals should be humanely euthanized and tested for rabies. PEP can be discontinued if the animal is proved by appropriate laboratory examination to be free of rabies

Potentially immunocompromized patients

- If CD4 < 200/mm³, use RIG in both category II and III exposure, even in previously immunized patients.
- A 3-visit vaccination schedule should be followed (ID or IM – D0, 7, 21-28) or a 2-visit schedule (ID or IM, D0, 7) with serological testing 2-4 weeks after first rabies vaccine administration to assess whether an additional vaccine administration is needed.

RIG

- Compartment syndrome may limit the amount of RIG that can be used when infiltrating fingers.
- Can be diluted with physiological buffered saline for large and multiple wounds.
Making things more complicated

Same protocol for category II and III exposure (ESSEN + RIG in naive patients and D0, 3 in immunized patients)

Naive individual

IM (1 ml)

4-dose ESSEN (US)

1x 1x 1x 1x

D0 D3 D7 D14

+ RIG in category II and III exposure

Immunized individuals

IM (1 ml)

1x 1x

D0 D3

RIG is not indicated
**Naive individual**

<table>
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<td>1x 1x 1x 1x</td>
<td>D0 D3 D7 D14 D21</td>
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</table>

+ RIG in category III exposure

**Immunized individuals**

| IM (1 ml) | 1x 1x | D0 D3 |
| ID (0.1 ml) | 1x 1x | D6 D3 |
| ID (0.1 ml) | 4x | D0 D3 D7 D21 |

RIG is not indicated

**Naive individual**

**Immunized individuals**

| IM (1 ml) | 1x 1x 1x 1x | D0 D3 D7 D21 |

+ RIG in category II and III exposure

RIG is not indicated

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Public Health
England

Guidelines on managing rabies post-exposure
June 2018

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ZAGREB

Naive individual

**IM (1 ml)**

2x 1x 1x 1x

D0 D3 D7 D14 D21

+ RIG in category III exposure
Thank you for your attention

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